containing 125 micrograms of clarithromycin per milliliter (estimated). Filter through a suitable filter capable of removing particulate matter 0.5 micron in diameter.

(ii) *Calculations.* Calculate the clarithromycin content as follows:

$$\text{Milligrams of clarithromycin per tablet} = \frac{A_U \times P_s \times d}{A_s \times 1{,}000 \times n}$$

where:

A_U = Area of the clarithromycin peak (at a retention time equal to that observed for the clarithromycin standard) in the chromatogram of the sample;

A_S = Area of the clarithromycin peak in the chromatogram of the clarithromycin working standard;

P_S = Clarithromycin activity in the clarithromycin working standard solution in micrograms per milliliter;

d = Dilution factor of the sample; and

n = Number of tablets in the sample.

(2) *Loss on drying.* Proceed as directed in § 436.200(c) of this chapter, using a sample weight of 1 to 2 grams.

(3) *Dissolution.* Proceed as directed in § 436.215 of this chapter. The quantity Q (the amount of clarithromycin dissolved) is 80 percent at 30 minutes.

(4) *Identity.* Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention time for the peak of the active ingredient must be within 2 percent of the retention time for the peak of the corresponding reference standard.

[58 FR 26654, May 4, 1993. Redesignated at 61 FR 34726, July 3, 1996]

§ 452.150b Clarithromycin granules for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Clarithromycin granules for oral suspension is a dry mixture containing clarithromycin-coated particles, suitable and harmless dispersing agents, diluents, preservatives, and flavorings. It contains the equivalent of 25 or 50 milligrams of clarithromycin activity per milliliter of the reconstituted suspension. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of clarithromycin that it is represented to contain. Its loss on drying is not more than 2.0 percent. When constituted as directed in the labeling, its pH is not less than 4.0 nor more than 5.4. The clarithromycin used conforms to the standards prescribed by § 452.50(a)(1).

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(A) The clarithromycin used in making the batch for potency, moisture, pH, residue on ignition, heavy metals, specific rotation, identity, and crystallinity.

(B) The batch for content, loss on drying, pH, and identity.

(ii) Samples, if required by the Director, Center for Drug Evaluation and Research:

(A) The clarithromycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(B) The batch: A minimum of six immediate containers.

(b) *Tests and methods of assay*—(1) *Clarithromycin content.* Proceed as directed in § 452.50(b)(1), except use a known injection volume between 10 and 60 microliters. Also, prepare the mobile phase, working standard solution, and sample solution, and use system suitability requirements and calculation as follows:

(i) *Mobile phase.* Add 600 milliliters of methanol and 400 milliliters of 0.067M potassium phosphate, monobasic, to a suitable container, mix well, and adjust the pH to 3.5 with phosphoric acid. Filter through a suitable filter capable of removing particulate matter to 0.5 micron in diameter. Degas the mobile phase just before its introduction into the chromatographic system.

(ii) *Preparation of standard solution.* Dissolve an accurately weighed portion of the clarithromycin working standard in sufficient methanol to obtain a solution having a known concentration of approximately 2.1 milligrams per milliliter of clarithromycin. Quantitatively transfer and dilute an aliquot of this solution with mobile phase and mix to obtain a solution of known

concentration of approximately 415 micrograms of clarithromycin per milliliter.

(iii) *Preparation of sample solution.* Constitute as directed in the labeling. Accurately measure a representative portion of the suspension that contains about 1 to 2 grams of clarithromycin activity and, using approximately 330 milliliters of 0.067M potassium phosphate, dibasic, quantitatively transfer into a 1,000 milliliter volumetric flask containing approximately 50 milliliters of 0.067M potassium phosphate, dibasic. Shake for 30 minutes. Dilute to volume with methanol. Mix well and place in an ultrasonic bath for 30 minutes. Cool to room temperature and adjust to volume with methanol. Add a magnetic stirring bar and stir for 60 minutes. Allow excipients to settle and dilute an appropriate aliquot of the solution with mobile phase to obtain a solution containing 500 micrograms of clarithromycin activity per milliliter and mix well. Filter through a suitable filter capable of removing particulate matter 0.5 micron in diameter.

(iv) *System suitability requirements*—(A) *Tailing factor.* The tailing factor (T) is satisfactory if it is not less than 1.0 and not greater than 1.7 for the clarithromycin peak.

(B) *Efficiency of the column.* The efficiency (n) is satisfactory if it is greater than 2,100 theoretical plates for the clarithromycin peak.

(C) *Capacity factor.* The capacity factor (k') is satisfactory if it is between 2.5 and 6 for the clarithromycin peak.

(D) *Coefficient of variation (relative standard deviation).* The coefficient of variation (S_R in percent of three replicate injections) is satisfactory if it is not more than 2.0 percent.

(v) *Calculations.* Calculate the clarithromycin content as follows:

$$\text{Milligrams of clarithromycin per milliliter} = \frac{A_U \times P_S \times D}{A_S \times V}$$

where:

A_U = Area of the clarithromycin peak in the chromatogram of the sample;

A_S = Area of the clarithromycin peak in the chromatogram of the clarithromycin working standard;

P_S = Clarithromycin activity in the clarithromycin working standard solution in micrograms per milliliter;

D = Dilution factor of the sample test solution; and

V = Volume, in milliliters, of the portion of suspension taken.

(2) *Loss on drying.* Proceed as directed in §436.200(a) of this chapter, using a sample weight of approximately 1 gram, weighing in a normal laboratory atmosphere.

(3) *pH.* Proceed as directed in §436.202 of this chapter, using the suspension prepared as directed in the labeling. Stir the suspension for 10 minutes with the electrode immersed and record the pH.

(4) *Identity.* Using the high-performance liquid chromatographic procedure described in paragraph (b)(1) of this section, the retention times for the clarithromycin peak must be within 2 percent of the retention time for the peak of the reference standard.

[61 FR 34726, July 3, 1996]

§452.160 Azithromycin oral dosage forms.

§452.160a Azithromycin capsules.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Azithromycin capsules are composed of azithromycin and one or more suitable and harmless diluents, disintegrants, lubricants, and wetting agents enclosed in a gelatin capsule. Each capsule contains azithromycin equivalent to 250 milligrams of azithromycin. The azithromycin content is satisfactory if it is not less than 90 percent and not more than 110 percent of the number of milligrams of azithromycin that it is represented to contain. The moisture content of the capsules is not more than 5.0 percent. The capsules pass the dissolution test.